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(54) Title: METHODS FOR DETECTING AND EVALUATING HEART DISORDERS

(57) Abstract

ECG signals are received from the patient (102), processed (103) to determine deviations from the normal and displayed (104) either as a frequency transformed signal or as a graph of the signal against one of its derivatives in a phase plane plot. The results, depending on the signal and circumstances may be interpreted to obtain information about heart disorders, the degree of drug toxicity or the efficacy of a particular drug. Further, an automatic defibrillator uses the ECG signal received (703) from the patient and processes (704) processing to determine the amount of energy to be discharged into the heart by the shock device (705).

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DESCRIPTION

Methods for Detecting and Evaluating Heart Disorders

Cross-Reference to Related Application

This application is a continuation-in-part of copending application S.N. 541,881, filed June 20, 1990 in the name of the same inventors and with the same title.

Background of the Invention

1. Field of the Invention

This invention relates to heart disorders. More specifically, this invention relates to detecting and evaluating arrythmia, fibrillation and related disorders by manipulation of an electrocardiogram signal.

2. Description of Related Art

Despite major advances in the diagnosis and treatment of ischemic heart disease over the past decade, a substantial number of patients each year may suffer sudden cardiac death as a consequence of ventricular fibrillation (VF). To date, no reliable predictive or preventive measures have been developed. By all outward appearances, VF is a highly complex, seemingly random phenomenon. So are other related heart disorders, including those stages in heart behavior which typically precede VF (onset of VF). Accordingly, it is difficult for automated devices to determine with any reliability that a patient is undergoing VF or onset of VF. Moreover, onset of VF may also be difficult to determine with any reliability, even for skilled medical personnel.

A method of detecting and evaluating heart disorders would therefore find wide applicability and utility. Patient monitoring devices may summon medical personnel if the patient is undergoing VF or onset of VF. Automatic

devices which attempt to counter VF, e.g. automatic implantable cardiac defibrillators (AICDs) may vary their operation based on evaluation of the severity of the patient's condition. Methods for reliably evaluating the risk of VF may also have important utility in monitoring patients undergoing surgery or other critical therapy.

It has been found that some anti-arrhythmic drugs may also have a pro-arrhythmic effect in excess concentrations. For example, quinidine has been known to be toxic in this manner. A method of detecting and evaluating heart disorders would also have wide applicability and utility in determining if a patient has been subjected to a toxic (or partially toxic) dosage of a drug relating to heart condition.

Chaos theory is a recently developed field relating to phenomena which appear to be highly complex and seemingly random, but which may be described as the deterministic result of relatively simple systems. Chaos theory may have potentially wide applications in biologic and other systems involving ambiguity and uncertainty. For example, it has been conjectured that chaos theory may be valuable for describing certain natural processes, including electroencephalogram (EEG) and electrocardiogram (EKG) signals. Techniques for detecting and evaluating aspects of deterministic chaos are known in the field of chaos theory, but have found little application in the medical field.

Accordingly, there is a need for improved methods and devices for detecting and evaluating heart disorders, including ventricular fibrillation (VF) and the onset of VF.

Summary of the Invention

A first aspect of the invention provides a method for detecting a heart disorder, by examination of a phase-plane plot (PPP) of a patient electrocardiogram (EKG). A normal patient will have a PPP which is relatively smooth;

a patient at risk of developing ventricular fibrillation (VF) onset will have a PPP which exhibits features of a chaotic process, such as multiple bands, "forbidden zones", periodicity with period-doubling and phase locking; a patient exhibiting VF will have a PPP which appears noisy and irregular. Differing PPPs may be readily recognized, thus detecting patients with heart disorders.

In a preferred embodiment, the PPP's degree of deterministic chaos may be measured by a processor, such as by graphic and numeric analysis. (1) The processor may measure a Lyapunov exponent or a fractal dimension of the PPP. (2) The processor may determine a Poincare section of the PPP and examine that Poincare section for indicators of deterministic chaos. Also, the processed PPP and Poincare sections may be reviewed by a human operator.

A second aspect of the invention provides a method for detecting a heart disorder, by examination of a frequency-domain transform (such as an FFT) of a patient EKG. A normal patient will have an FFT with a discrete spectrum, while a patient exhibiting VF will have an FFT with a relatively continuous spectrum and a peak energy at a relatively low frequency (e.g., about 5-6 Hz). A patient exhibiting VF which is difficult to revert with shock will have an FFT with a peak energy at a relatively high frequency (e.g., about 10 Hz or more).

In a preferred embodiment, an automatic defibrillating device may comprise means for delivering a variable shock, the size of which is determined at least in part by the FFT's peak energy. The defibrillating device may also comprise means for signalling an alarm if the FFT's peak energy is at a relatively high frequency.

A third aspect of the invention provides a method for detecting drug toxicity, based on particulars of an action-potential duration (APD) restitution curve, or an action-potential amplitude (APA) curve, which is con-

structed for the patient, such as fitting an exponential relation to that curve or such as a parameter time constant for that curve. The slope of the fitted curve will indicate the patient's possibility of predisposition to arrythmia. Differences in the parameters of the fitted curve allow one to distinguish between normal and abnormal patients, e.g. those at risk of arrythmia or ischemia. A normal patient will have a relatively low parameter time constant; a patient who is exhibiting drug toxicity will have a relatively high parameter time constant. A PPP of APD or APA data may also be generated, and the analytical techniques described herein may be utilized to interpret that PPP, to determine and evaluate drug toxicity.

Brief Description of the Drawings

Figure 1 shows a patient monitoring system.

Figure 2 shows a set of sample EKG signals.

Figure 3 shows a set of corresponding PPPs for the sample EKG signals of figure 2.

Figure 4 shows an example PPP and a corresponding Poincare section.

Figure 5 shows an example PPP and a corresponding time-lapse Poincare section.

Figure 6 shows a set of corresponding frequency-domain transforms, obtained by performing a fast Fourier transform (FFT) on the EKG signal.

Figure 7 shows an improved automatic implantable cardiac defibrillator ("AICD").

Figure 8 shows a signal response of an individual heart muscle cell to a stimulus, known in the art as "action potential".

Description of the Preferred Embodiment

A first aspect of the invention relates to detection and evaluation of heart disorders by examination of a phase-plane plot (PPP) of a patient electrocardiogram (EKG).

Figure 1 shows a patient monitoring system. A patient 101 is coupled to an electrocardiogram (EKG) device 102, which acquires EKG signals and transmits them to a processor 103. The processor 103 may display the EKG signals on a monitor 104 (as is well-known in the art), or it may process the EKG signals and display any results of processing on the monitor 104.

EKG signals are well-known in the art, as are methods of acquiring them. As used herein, an EKG refers to a surface electrocardiogram, but other forms of electrocardiogram would also work with the methods disclosed herein, and are within the scope and spirit of the invention. For example, the EKG shown herein may comprise a surface EKG, an epicardial EKG, an endocardial EKG, or another related signal (or set of signals) measured in or near the heart. Moreover, the signal which is manipulated may be a voltage signal, a current signal, or another related electromagnetic values (or set of values).

Figure 2 shows a set of sample EKG signals. A first EKG signal 201 shows a normal patient. A second EKG signal 202 shows a patient in transition to VF. A third EKG signal 203 shows a patient with VF.

The processor 103 may construct a phase-plane plot (PPP) from the EKG signal. A first type of PPP comprises a plot of an EKG variable against its first derivative. In a preferred embodiment, the EKG variable is voltage, v (itself a function of time); its first derivative is dv/dt (also a function of time).

However, it would be clear to one of ordinary skill in the art, after perusal of the specification, drawings and claims herein, that wide latitude in construction of the PPP is possible. The variable chosen for the PPP may be any one of a variety of different parameters, including EKG voltage, current, or another signal value. The chosen variable (v) may be plotted against its first time derivative (dv/dt), its second time derivative d^2v/dt^2, or

another time derivative $d^n v/dt^n$. Or, an Mth derivative may be plotted against an Nth derivative.

Another type of PPP may comprise a plot of an EKG variable (or an Nth derivative thereof) against a time delayed version of itself, (e.g. v(t) versus v(t-δt)). This type of PPP is sometimes also called a "return map". This type of PPP is less sensitive to EKG signal noise.

Another type of PPP may comprise a plot of three EKG variables (or Nth derivatives thereof) simultaneously (e.g., v, dv/dt, and d^2v/dt^2). Such a PPP would be 3-dimensional. Where the PPP is 3-dimensional, it may be displayed stereoscopically, or a 2-dimensional plane "cut" of the 3-dimensional display may be displayed on a 2-dimensional display. It would be clear to one of ordinary skill in the art, that all of these choices described herein, or combinations thereof, would be workable, and are within the scope and spirit of the invention.

Figure 3 shows a set of corresponding PPPs for the sample EKG signals of figure 2. A first PPP 301 corresponds to the first EKG signal 201. A second PPP 302 corresponds to the second EKG signal 202. A third PPP 303 corresponds to the third EKG signal 203.

Part of this aspect of the invention is the discovery that a normal patient will have a PPP which exhibits the regularity and smoothness of an EKG signal from that normal patient, while a patient undergoing VF will have a PPP which exhibits the irregularity and complexity of an EKG signal which might be deterministic chaos (e.g., a periodicity, banding and "forbidden zones"). Moreover, a patient in transition from normal into VF (i.e., in VF onset) exhibits a PPP which is consistent with an assessment that the EKG signal for the patient is in transition to deterministic chaos.

A normal patient has a relatively regular beat-to-beat EKG signal. As the patient transitions to VF, the patient's EKG signal at first shows oscillations between pairs of alterant regular beat-to-beat signals. As the

transition continues, the patient's EKG signal then shows oscillations between greater and greater numbers of alterant regular signals (e.g., four possible alternants, eight possible alternants, etc.), until it is no longer possible to identify alterant regular signals and the EKG signal is irregular and highly complex. At that point, the patient is generally said to be exhibiting VF.

In like manner, the patient's PPP will transition from a smooth single-banded display, through a multi-banded display (showing multiple alternants) and finally to an irregular and highly complex display. The display change in the PPP is so striking that even a relatively untrained person can see the difference. This is in contrast with display changes in the EKG, which generally requires a skilled cardiologist to evaluate.

There are several possible factors which might cause a patient to transition from normal to VF. These factors may include drug overdose (especially overdose with an anti-arrhythmic which has a pro-arrhythmic effect in overdosage, e.g., quinidine intoxication), excessive electrical stimulation, hypothermia, ischemia, and stress. In a preferred embodiment, a patient monitor may examine the patient's PPP so as to determine if the patient is in transition from normal to VF; this could indicate that one of these pro-arrhythmic factors is excessively present.

The processor 103 may further process the PPP so as to measure the PPP's degree of deterministic chaos. Several techniques may be applied for this purpose:

(1) The processor 103 may measure a Lyapunov exponent of the PPP. The Lyapunov exponent of the PPP is a measure of the degree to which nearby paths of the PPP diverge. The Lyapunov exponent is well-known in chaos theory and may be measured with available software. See, e.g., Wolf et al., "Determining Lyapunov exponents from a time series", Physica D 1985;16:285-317.

(2) The processor 103 may measure a fractal dimension of the PPP. The fractal dimension of the PPP is a measure of the degree to which the PPP forms a "space-filling" curve. The fractal dimension is well-known in chaos theory and may be measured with several techniques (e.g. correlation dimension or box-counting methods), for example as shown below:

To measure the fractal dimension of the PPP, the processor 103 superimposes a rectilinear grid (comprising a set of boxes) on the PPP and counts the number of boxes which are cut by the PPP's trace. The processor 103 varies the size of the grid and records each grid size and each count. The processor 103 then computes the constant k in the following relation:

ln (# of boxes cut) = k * ln (# of boxes in grid) (304)

The constant k is a measure of the fractal dimension of the PPP. A value of k between about 3 and about 7, especially with a fractional component, implies that the PPP is likely to represent a process based on deterministic chaos, and therefore a patient who is close to (or actually in) VF.

(3) The processor 103 may determine a Poincare section of the PPP and examine that Poincare section for indicators of deterministic chaos, as described herein. The processed PPP and Poincare sections may also be displayed for review by a human operator, whereupon any visible structure will be readily recognized.

Figure 4 shows an example PPP 401 and a corresponding Poincare section 402. A Poincare section may comprise a line segment drawn across a part of the PPP. In general, such a line segment will be close to perpendicular to the trajectories of the PPP in a region of interest.

The processor 103 may acquire the data points in each Poincare section or PPP and compute a statistical measure of anisotropy or inhomogeneity of those data points. One such measure is based on the mean and standard deviation

of those data points (these may be computed by statistical methods which are well-known in the art). The ratio

r = (standard deviation) / (expected value) (403)

is a measure of the degree of clumping in the Poincare section.

A greater value for r implies that the PPP is more likely to represent a process based on deterministic chaos, and therefore a patient who is close to (or actually in) VF. The value for r may be displayed for review by a human operator in comparison with a value for r for a normal patient, together with a set of confidence bands, as is well-known in the art, for indicating a degree of variation from a normal patient.

The processor 103 may also compute other statistical measures of the Poincare section.

The processor 103 may also determine a "time-lapse" Poincare section of the PPP.

Figure 5 shows an example PPP 501 and a corresponding time-lapse Poincare section 502. A time-lapse Poincare section may comprise a set of data points selected from the PPP by selecting one data point every t seconds. The time-lapse Poincare section may be analyzed in like manner as the other Poincare section disclosed herein.

A second aspect of the invention relates to detection and evaluation of heart disorders based on a frequency-domain transform of a patient EKG.

Figure 6 shows a set of corresponding frequency-domain transforms, obtained by performing an FFT on the EKG signal. A first transform 601 corresponds to a first EKG signal (not shown). A second transform 602 corresponds to a second EKG signal (not shown).

In the first transform 601, representing a normal patient, the frequency spectrum shows that the energy of the corresponding EKG signal occurs primarily at a discrete set of frequencies. In the second transform 602, representing a patient exhibiting VF, the frequency spectrum shows that the energy of the corresponding EKG

signal has a continuous spectrum of frequencies, and has an energy peak 603.

Part of this aspect of the invention is the use of both visual and mathematical techniques for analyzing frequency domain transforms, including for example calculation of a harmonic magnitude ratio (HMR). To determine the HMR, a major peak or a central region of energy distribution in a spectrum of a frequency domain transform (such as an FFT) may be identified, and the HMR calculated as follows: A magnitude of the transform in the region of the identified point is determined (e.g., by summing the magnitude of the transform at the identified point and at surrounding points), and is summed with the corresponding magnitude in the region of harmonic values of the frequency for the identified point. This sum is divided by a total magnitude of the transform for the entire signal; the ratio is defined as the HMR.

One method which is known for bringing a patient out of VF ("defibrillating") is to administer an electric shock across the patient's heart. This electric shock must generally have a substantial energy, e.g. 10-20 joules, and may often cause tissue damage to the patient even if it is successful in defibrillating the patient. Multiple shocks may be required, generally of increasing energy. Accordingly, it would be advantageous to use a larger shock only when necessary, and it would be advantageous to use as few shocks as possible.

Part of this aspect of the invention is the discovery that when the energy peak 603 of the frequency-domain transform 602 is at a relatively low frequency, a relatively low energy shock will generally suffice to defibrillate the patient. When the energy peak 603 of the frequency-domain transform 602 is at a relatively high frequency (also, when a secondary energy peak 604 appears in the frequency-domain transform 602 at a relatively high frequency), it will require a relatively high energy shock to defibrillate the patient, if it is possible to

defibrillate the patient by means of an electric shock at all.

One application of this discovery is in automated implanted cardiac defibrillators (AICDs), which attempt to automatically detect VF and to automatically administer a shock to defibrillate the patient.

Figure 7 shows an improved AICD 701. A patient 702 is coupled to an AICD EKG 703, which acquires EKG signals and transmits them to an AICD processor 704, which controls a shock device 705 for administering a defibrillating shock to the patient 702.

The improved AICD 701 also comprises (e.g., as part of the AICD processor 704) software for determining an FFT of the EKG signal and for determining the energy peak in that FFT. If the energy peak in that FFT is relatively low, the AICD processor 704 controls the shock device 705 to administer a relatively small shock to the patient. If the energy peak in that FFT is relatively high, the AICD processor 704 controls the shock device 705 to administer a relatively large shock to the patient, and may also signal an alarm 706 or other indicator that defibrillation may not be successful.

A third aspect of the invention relates to detection and evaluation of drug toxicity based on a parameter time constant for an action-potential duration (APD) restitution curve or an action-potential amplitude (APA) curve which is constructed for the patient.

Figure 8 shows a signal response of an individual heart muscle cell to a stimulus. This individual cell response is known in the art as "action potential".

It is well-known in the art that a time duration for recovery 801 of an individual cell depends on factors including a resting period 802 which the cell has had prior to stimulus. It is also well-known in the art that an APD restitution curve can be constructed for a human patient with the use of an intracardiac catheter. However, the complete relation between the actual time

duration for recovery 801 based on the resting period 802 is not known.

Part of this aspect of the invention is the discovery that when the time duration for recovery 801 is plotted against the resting period 802 (diastolic interval), the curve follows an exponential relation:

$$APD = APD_{pl} - A * \exp(-DI/tau) \quad (803)$$

where APD_{pl} is the plateau APD, A is a proportionality constant, DI is the diastolic interval, and tau is the parameter time constant

The nonlinear nature of the APD restitution curve may promote deterministic chaos in response to excessive stimulus of the heart muscle cells. When the APD restitution curve is steeper (i.e., the parameter time constant tau is larger), there is accordingly a greater predilection for the heart to enter VF. Thus, another part of this aspect of the invention is the discovery that a normal patient will have a relatively low APD restitution parameter time constant, while a patient who is exhibiting drug toxicity (e.g., quinidine intoxication) will have a relatively high APD restitution parameter time constant. The restitution parameter time constant may also be used in monitoring cardiac stability, and in evaluating efficacy of anti-arrhythmic drugs.

Experimental verification of the present invention has been achieved by the inventors.

Experiment I.

A mathematical study used PPPs, return maps, Poincare sections, correlation dimension, and spectral analysis to distinguish periodic, chaotic and random signals. PPPs were useful in distinguishing among all three classes of signals. Periodic signals showed clear, widely separated trajectories; chaotic signals showed banding, forbidden zones and sensitive dependence on initial conditions; random signals showed no clear internal structure. With the exception of noise effects, the only major difference

between the PPPs and the appropriately lagged return map was a 45 degree rotation. Poincare sections were also able to distinguish among the three classes of signals: periodic signals showed isolated points; chaotic signals showed ordered areas of apparent self-similarity; random signals showed a Gaussian distribution of points. Correlation dimension was more able to distinguish between chaotic and random signals than between chaotic and periodic signals. Spectral analysis using FFTs and harmonic magnitude ratio (HMR) was able to distinguish periodic signals, but were unable to distinguish between random and chaotic signals: HMRs of periodic signals were greater than 97%; HMRs of chaotic signals varied between 17 and 80%; HMRs of random signals were approximately 40%. PPPs were greatly affected by noise, return maps were less affected, while spectral analysis was relatively immune to noise. It was concluded that PPPs, return maps, Poincare sections, correlation dimension and spectral analysis are all useful determinatives of chaotic systems.

Experiment II.

A mathematical study concentrated specifically on ability of spectral analysis to distinguish chaotic from random signals. In this experiment, two series of random signals were generated. The first series comprised 5000 pseudo-random numbers which were smoothed using a method of least-squares approximation. The second series comprised white noise obtained from an analog-to-digital conversion board. Spectral analysis was performed by applying an FFT to the data, and searching for a broad band spectrum or a change from a narrow band to a broad band, which was presumed to be diagnostic of chaos. It was concluded that spectral analysis by itself was insufficient to unequivocally distinguish chaotic signals from random signals, and that additional tests such as PPPs and return maps were necessary for this purpose.

Experiment III.

An experiment examined spectral analysis, visualization of PPPs and correlation dimension analysis, for usefulness in distinguishing between normal sinus rhythm and VF in dogs. Ischemia and re-perfusion were used as stress factors in closed-chest anesthetized dogs. Spectral analysis of the dogs having normal sinus rhythm revealed narrow-band spectra with fundamental frequencies at the sinus rate and harmonics extending beyond 50 Hz. PPPs were consistent with periodic dynamics, and dimension analysis revealed low dimensional behavior (1--2.5). In contrast, spectral analysis of the dogs having VF, revealed broad-band behavior with most of the energy at 6 Hz, and with energy at all frequencies between 1 and 25 Hz. PPPs showed constrained aperiodic behavior, and the dimensional analysis revealed higher dimensions (4-6) than that observed for the normal sinus rhythm dogs. Thus, all three techniques proved useful in distinguishing normal sinus rhythm from VF.

Experiment IV.

An experiment examined spectral analysis, visualization of PPPs, visualization of return maps, and correlation dimension analysis, for their usefulness in identifying VF in humans. These analytical techniques were applied to data from eight hypothermic patients undergoing spontaneous VF, and also to data from three normothermic patients with VF induced during electrophysiology testing. All patients had a broad band frequency spectrum (0-12 Hz), a low dimension (range 2-5), and banding and forbidden zones on PPPs and return maps. It was concluded that spectral analysis, visualization of PPPs, visualization of return maps, and correlation dimension analysis are useful in detecting and evaluating VF.

Experiment V.

An experiment examined spectral analysis, visualization of PPPs and correlation dimension analysis for their usefulness in distinguishing between normal sinus rhythm and VF in humans. VF in eight hypothermic human patients undergoing open-heart surgery was studied. In all patients, first and second order PPPs showed forbidden zones and banding, and an FFT revealed a relatively continuous power spectrum at all frequencies from zero to 25 Hz, with a majority of the power below 12 Hz. In contrast, correlation dimension in all cases was less than 4. It was concluded that multiphasic analysis of the data is preferable to reliance on a single analytical technique such as correlation dimension.

Experiment VI.

An experiment utilized spectral analysis and visualization of PPPs to elucidate the heterogenous nature of atrial fibrillation. In the experiment, the researchers induced acute fibrillation by a rapid train of stimuli to the atria of seven closed-chested dogs. PPPs based on the EKG data often inscribed well defined structures, and an FFT of the digitized EKGs showed peaks mostly below 15 Hz that were either discrete with clear harmonic components, or had continuous spectra that changed in a time- and site-dependent manner. It was concluded that both spectral analysis and visualization of PPPs are useful techniques for analyzing atrial as well as ventricular fibrillation.

Experiment VII.

In an experiment, visual analysis of PPPs and the slope of an APD restitution curve were found to be useful for detecting and evaluating quinidine-induced VF in in vivo hearts. Quinidine was administered at 30 minute intervals over five hours, until either a total of 90-100 mg/kg was administered or until ventricular tachycardia or

VF occurred, whichever came first. PPPs of the quinidine intoxicated cells demonstrated sensitive dependence on initial conditions and the presence of forbidden zones, and the corresponding FFTs showed continuous spectra. In contrast, PPPs of cells in a control dog were uniform and densely packed, and the corresponding FFTs showed discrete spectra. The initial slope of the APD restitution curve of quinidine intoxicated cells was much steeper, by at least an order of magnitude, than the slope of normal cells. It was concluded that quinidine toxicity correlates with the slope of the APD restitution curves.

Experiment VIII.

An experiment compared the slope of the APD and APA restitution curves with quinidine intoxication. Quinidine was administered (90-100 mg/kg) to eight dogs over a five hour period. Three untreated dogs served as controls. Ventricular and Purkinje cells from both treated and untreated dogs were then subjected to electrical stimulation with cycles from 900 to below 600 msec. Shortening of the cycle length to 600 msec resulted in irregular dynamics of both APD and APA, including electrical alternans and bifurcation. The slope of an APD restitution curve was calculated, and found to be steeper in quinidine-intoxicated cells for both Purkinje fibers and ventricular muscle cells than the slope during quinidine washout or in normal untreated cells. The curve could be fit by the exponential equation given herein. APA changes were almost always correlated with the APD changes. In the three normal tissue preparations neither ventricular muscle cells nor Purkinje cells showed bifurcative behavior with respect to APD or AA. It was concluded that quinidine toxicity, and presumably other drug-induced pro-arrhythmic effects, correlate with the slope of both APD and APA restitution curves.

Experiment IX.

In an experiment, quinidine-induced ventricular tachycardia and VF in dogs was analyzed using PPPs generated from action potential duration (APD) and action potential amplitude (APA) data. Both PPPs showed forbidden zones and sensitive dependence on initial conditions which are indicative of chaos. It was concluded that PPPs based on either APD or APA are useful in detecting and evaluating quinidine toxicity.

Experiment X.

In an experiment, EKGs of quinidine intoxicated dogs were analyzed by frequency spectra, phase plane plots, Poincare sections, return maps and Lyapunov exponents. In the control state and at therapeutic doses, PPPs were uniformly thick and showed no gaps, indicating that cycle-to-cycle variation was due to normal biological "noise". But as the quinidine dose was increased to intermediate levels (40-50 mg/kg), PPPs showed clear non-uniform thickening, indicating sensitive dependence on initial conditions, and also showed marked banding (densely filled regions separated by divisions or gaps). At these intermediate doses, Lyapunov exponents became positive and Poincare return maps also indicated nonrandom chaos. At still higher doses, PPPs became more complex. In two dogs that did exhibit VF (and not in another) there was a significant change in the PPP at the last pre-fibrillatory dose: the development of a "funnel", a classic mechanism of chaos. Frequency spectra at all pre-fibrillatory doses were discrete, with peaks at a fundamental frequency and multiple harmonics. It was concluded that chaos does occur during progressive quinidine intoxication, and that PPPs, and graphic and numeric analysis based on the PPPs, are better indicators of chaos than frequency spectra.

Experiment XI.

In an experiment, quinidine toxicity in dogs was analyzed using PPPs generated from APA and APD data. EKG recordings were made at various driving rates from 1000 to 500 msec. Increase in the driving rate from 1000 to 500 msec caused the progressive appearance of higher order periodicities (period 3 and 4). Phase locking was seen with a stimulus (S) response (R) pattern repeating periodically in all 4 preparations at S:R ratios of 2:1, 5:3, 3:2. At faster drive rates aperiodic variations in APA and APD were observed. A number of intermediate stages that presage chaos were also seen in the quinidine intoxicated fibers. These results further demonstrate the usefulness of the methods of the present invention to detect both quinidine intoxication and precursor stages to intoxication.

Experiment XII.

In an experiment, quinidine toxicity in dogs was analyzed using PPPs generated from APA and APD data. Electrical stimuli were used to drive cardiac tissue at various rates from 2000 to under 300 msec. These stimuli caused steady alternans (bifurcation) in APD and APA of 108 ± 36 msec and 12 ± 9 millivolts respectively. Further increase in driving rates gave rise to irregular dynamics. This transition was preceded by various repeating stimulus-response ratios (phase-locking) for up to fifty consecutive beats. No such dynamics could be induced in three non treated (control) tissues. The APD restitution curve had significantly ($p < 0.05$) steeper slope than six control fibers. Stimulus-response latency remained constant at 6-9 msec. PPPs of the APDs during the irregular dynamics showed sensitive dependence on initial conditions and forbidden zones consistent with chaos theory. These results further demonstrate the usefulness of the methods of the present invention to detect both

quinidine intoxication and precursor stages to intoxication.

Experiment XIII.

An experiment used spectral analysis, PPPs, Poincare sections, Lyapunov Exponents and dimension analysis to analyze computer simulated waveforms including sine waves, modulated sine waves, square waves, saw toothed waves, and triangular waves. The researchers added random noise to the waveforms at 1%, 10% and 20%. The experiment further used the same analytical techniques on EKG data from anesthetized dogs in which VF was precipitated by five different interventions: quinidine intoxication; premature electrical stimulation followed by quinidine intoxication; coronary occlusion; reperfusion of acutely ischemic myocardium; and global hypothermia. The preliminary results showed that PPPs and Poincare sections in dogs undergoing ventricular fibrillation were consistent with chaos, while spectral analysis was not suggestive of chaos. The researchers concluded in part that VF can be described as chaotic electrophysiological behavior, but that single methods of analysis are not sufficient to detect such behavior.

One conclusion which may be drawn from the research cited herein is that the analytical value of each of the aspects of the invention may be enhanced through combination with one or more of the other aspects of the invention. A preferred embodiment of the present invention may include a combination of the aspects of the invention described herein. One preferred embodiment may comprise multiphasic analysis of a PPP (e.g., visually with a display, graphically with Poincare sections, and numerically with Lyapunov exponents and correlation dimension), frequency spectral analysis, and mathematical analysis of an APD restitution curve.

Alternative Embodiments

While preferred embodiments are disclosed herein, many variations are possible which remain within the concept and scope of the invention, and these variations would become clear to one of ordinary skill in the art after perusal of the specification, drawings and claims herein.

It would also become clear to one of ordinary skill in the art that embodiments of the invention may comprise means for continuous monitoring of drug toxicity, atrial fibrillation, ischemia or other heart conditions, such as during surgery or patient recovery from surgery. Moreover, embodiments of the invention may comprise means for indicating heart conditions which are detected to attending medical personnel or to the patient. In one preferred embodiment of the invention, means may be provided for directing the patient (when a heart disorder is detected) to contact a physician or to proceed to a nearby hospital for treatment.

Claims

1. A method for detecting heart disorders, comprising the steps of

receiving an electrocardiogram signal;

determining a phase-plane plot of said electrocardiogram signal; and

determining if said phase-plane plot indicates a heart disorder.

2. A method as in claim 1, wherein said heart disorders are one of the group: ischemia, electrical instability, drug toxicity.

3. A method as in claim 1, wherein said phase-plane plot comprises a multi-dimensional plot of at least two variables.

4. A method as in claim 1, wherein said phase-plane plot comprises a multi-dimensional plot of at least three variables.

5. A method as in claim 1, wherein said phase-plane plot comprises a plot of a signal voltage against a derivative of said signal voltage.

6. A method as in claim 5, wherein said derivative is a first derivative.

7. A method as in claim 1, wherein said step of determining if said phase-plane plot indicates a heart disorder comprises the step of determining a fractal dimension of said phase-plane plot.

8. A method as in claim 1, wherein said step of determining if said phase-plane plot indicates a heart disorder comprises the step of determining a Lyapunov exponent of said phase-plane plot.

9. A method as in claim 1, wherein said step of determining if said phase-plane plot indicates a heart disorder comprises the step of determining the presence of at least one of: banding, forbidden zones, nonuniform thickening, periodicity, aperiodicity.

10. A method as in claim 1, wherein said step of determining if said phase-plane plot indicates a heart disorder comprises the step of determining the presence of multiple alternants.

11. A method for detecting heart disorders, comprising the steps of

receiving an electrocardiogram signal;

determining a phase-plane plot of said electrocardiogram signal;

determining a Poincare section of said phase-plane plot; and

determining if said Poincare section indicates a heart disorder.

12. A method as in claim 11, wherein said phase-plane plot comprises a multi-dimensional plot of at least two variables.

13. A method as in claim 11, wherein said phase-plane plot comprises a multi-dimensional plot of at least three variables.

14. A method as in claim 11, wherein said phase-plane plot comprises a plot of a signal voltage against a derivative of said signal voltage.

15. A method as in claim 14, wherein said derivative is a first derivative.

16. A method as in claim 11, wherein said step of determining if said Poincare section indicates a heart disorder comprises the step of determining a statistical measure of at least one of: anisotropy, inhomogeneity.

17. A method for detecting heart disorders, comprising the steps of

receiving an electrocardiogram signal;

determining a frequency domain transform of said electrocardiogram signal;

determining if said frequency domain transform indicates a heart disorder.

18. A method as in claim 17, wherein said step of determining a frequency domain transform comprises the step of performing a Fourier transform.

19. A method as in claim 17, wherein said step of determining if said frequency domain transform indicates a heart disorder comprises the step of determining if said frequency domain transform comprises a continuous spectrum.

20. A method as in claim 17, wherein said step of determining if said frequency domain transform indicates a heart disorder comprises the step of determining if said frequency domain transform comprises an energy peak at a relatively high frequency.

21. A method as in claim 20, wherein said relatively high frequency is greater than about 6 Hz.

22. A method as in claim 20, wherein said relatively high frequency is greater than about 10 Hz.

23. An automated implantable cardiac defibrillator, comprising

means for receiving an electrocardiogram signal from a patient;

means for administering a defibrillating shock from said patient;

means for processing said electrocardiogram signal and for controlling said means for administering, wherein said means for processing causes said means for administering to administer a shock whose energy depends on a frequency domain transform of said electrocardiogram signal.

24. A defibrillator as in claim 23, wherein said energy is relatively greater when said frequency domain transform has an energy peak at a relatively greater frequency.

25. A method for detecting drug toxicity for a patient, comprising the steps of

constructing a relation between a diastolic interval and an action potential duration for said patient;

determining a value of a time constant for said relation; and

determining if said value indicates drug toxicity.

26. A method as in claim 25, wherein said step of determining if said value indicates drug toxicity comprises the step of determining if said value is substantially above a normal value.

27. A method for evaluating effectiveness of a drug for a patient, comprising the steps of

constructing a relation between a diastolic interval and an action potential duration for said patient;

determining a value of a time constant for said relation; and

determining if said value indicates that administration of said drug to said patient has an anti-arrhythmic effect.

28. A method for evaluating effectiveness of a drug for a patient, comprising the steps of

determining a set of action potential duration restitution data for said patient;

constructing a phase plane plot from said data; and

performing a multiphasic analysis of said phase plane plot to determine if said phase plane plot indicates that administration of said drug to said patient has an anti-arrhythmic effect.

29. A method as in claim 28, wherein said multiphasic analysis comprises at least one step of displaying said phase plane plot, computing a Poincare section of said phase plane plot, computing a Lyapunov exponent of said phase plane plot, or computing a correlation dimension of said phase plane plot.

30. A method for detecting heart disorders, comprising the steps of

receiving an electrocardiogram signal;

performing a plurality of the following steps to determining if said electrocardiogram signal indicates a heart disorder: (a) performing a multiphasic analysis of a phase-plane plot of said electrocardiogram signal, (b) performing a spectral analysis of said electrocardiogram signal, or (c) performing an analysis of an APD restitution curve computed in response to said electrocardiogram signal.

31. A method as in claim 30, wherein said step of performing a spectral analysis comprises the step of calculation of a harmonic magnitude ratio.

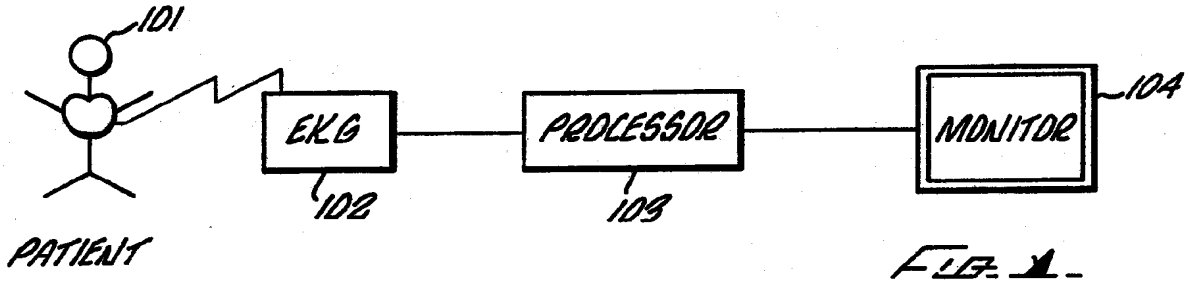


FIG. 1.

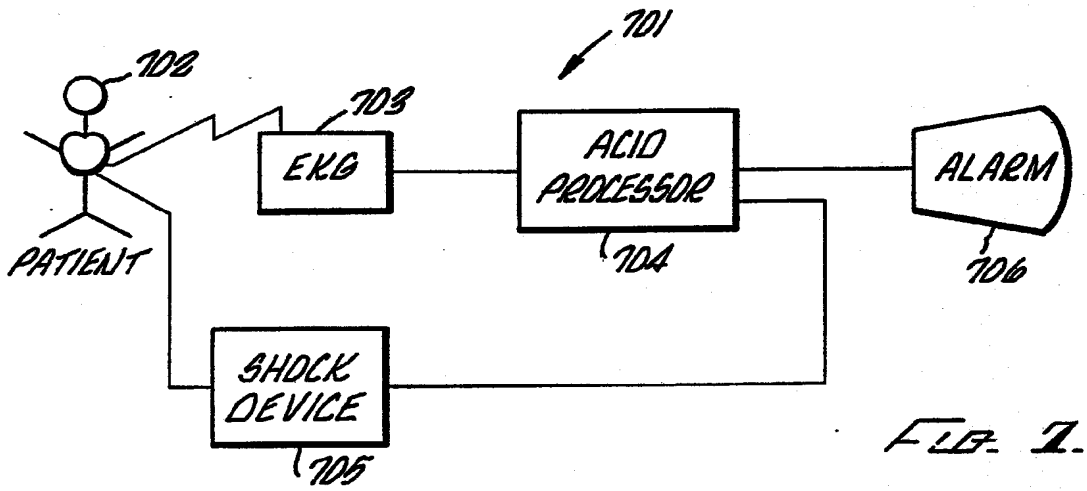


FIG. 7.

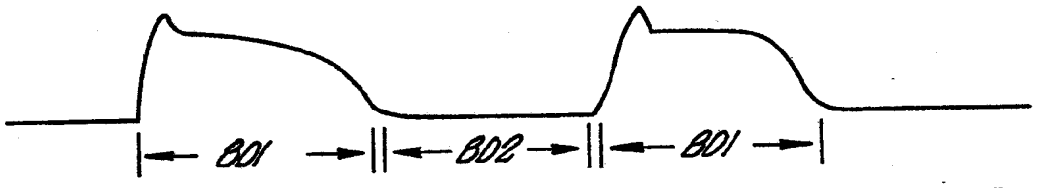


FIG. 8.

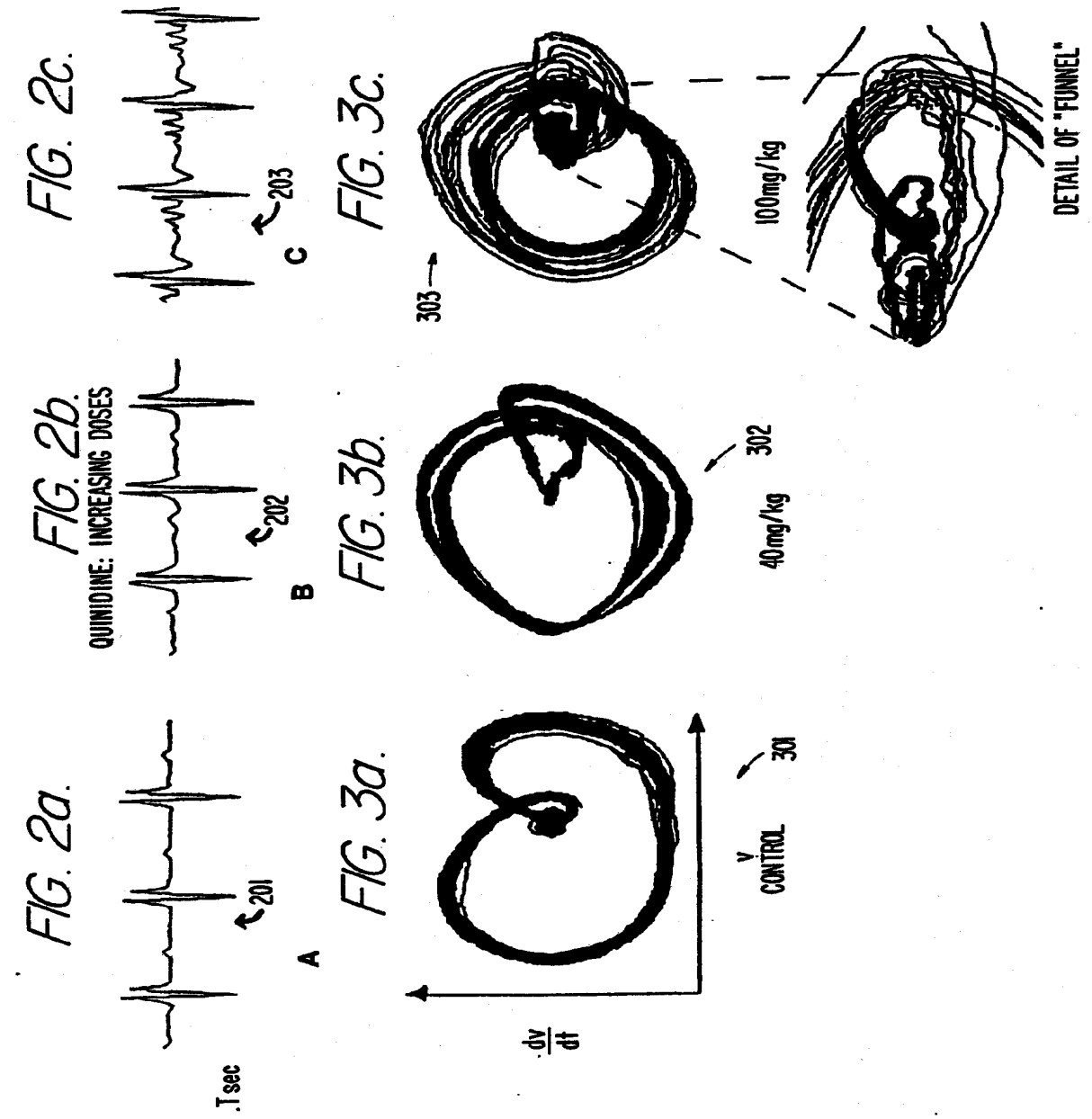
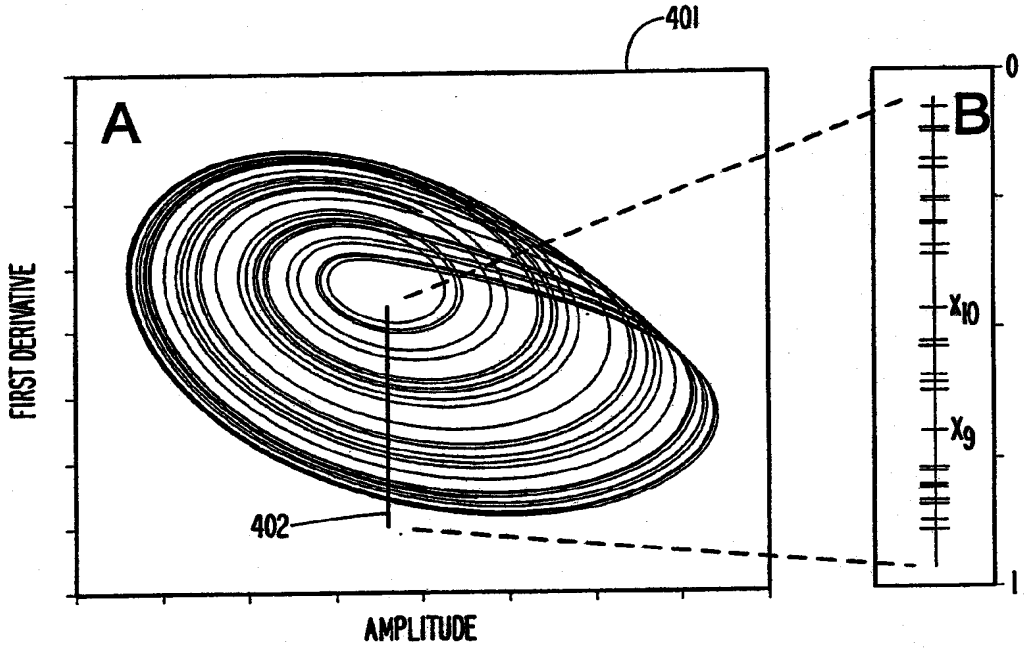


FIG. 2a.
201
A
1 sec
FIG. 2b.
QUINIDINE: INCREASING DOSES
202
B
FIG. 2c.
203
C
FIG. 3a.
dV/dt
V
CONTROL
301
FIG. 3b.
302
40mg/kg
FIG. 3c.
303
100mg/kg
DETAIL OF "FUNNEL"

FIG. 4.



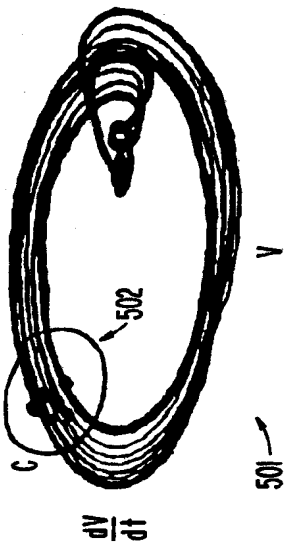


FIG. 5.

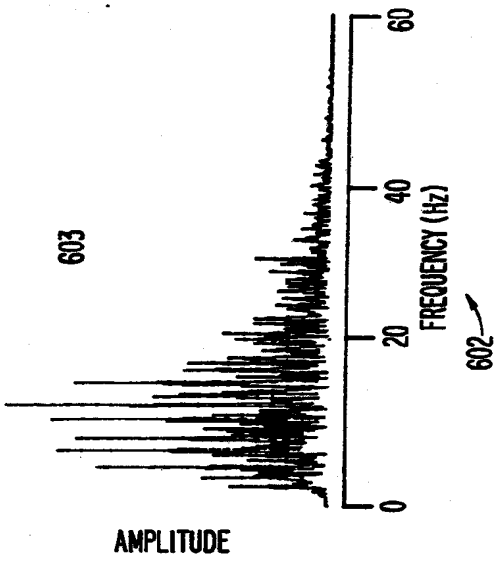


FIG. 6b.

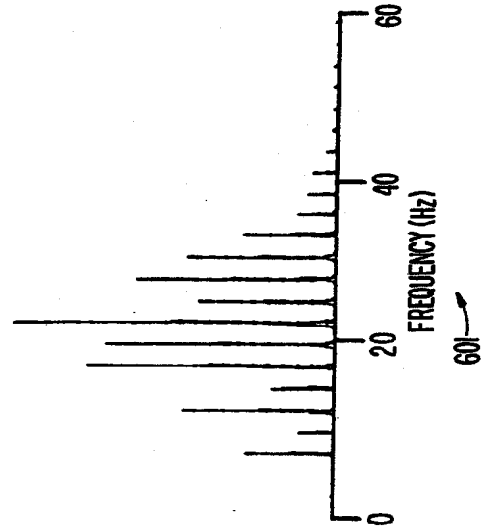


FIG. 6a

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/04000

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5) A61B 5/044
US CL. 128/712

II FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	128/419D,696,699,700,702-704 364/413.05,413.06 424/2,9,10 424/2,9 514/259,596,821

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	US,A 3,929,125 BARNES et al 30 December 1975	1-16,30-31
A	US,A 3,940,692 NEILSON 24 FEbruary 1976	1-16,30-31
A	US,A 4,085,407 STRATBUCKER et al 18 April 1978	1-16,30-31
A	US,A 4,570,225 LUNDY 11 February 1986	1-16,30-31
A,E	US,A 4,979,110 ALBRECHT et al 18 December 1990	17-22
A	US,A 4,680,708 AMBOS et al 14 July 1987	17-22
X	US,A 4,924,875 CHAMOUN 15 May 1990 (See Abstract)	17-22
A,P	US,A 4,974,598 JOHN 04 December 1990 (See Fig. 3 and col. 8, lines 21-68)	17-22
Y	US,A 4,523,595 ZIBELL 18 June 1985 (Fig. 11d & col. 13, lines 20-68)	23-24
Y	US,A 4,403,614 ENGLE et al 13 September 1983 (See col. 8, lines 52-67)	23-24
A	US,A 4,384,585 ZIPES 24 May 1983	23-23

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
11 August 1991	18 NOV 1991
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	William E. Kamm

Form PCT/ISA/210 (second sheet) (May 1986)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [1] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [1], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

I. Claims 1-16, 30-31 drawn to a phase plane plot diagnostic method.
II. Claims 17-22 drawn to a frequency of main diagnostic method.
III. Claims 23-24 drawn to a defibrillator
IV. Claims 25-26 drawn to a drug toxicity test
V. Claims 27-29 drawn to a drug efficency test

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers [illegible] claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international [illegible] those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search [illegible] the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Aut [illegible] invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
A	US,A 4,673,563 BERNE et al 16 June 1987	25-29
A	US,A 4,377,592 AUROUSSEAU 22 March 1983	25-29